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Population-Based Assessment of Hospitalizations for Toxicity From Chemotherapy in Older Women With Breast Cancer

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Abstract

Purpose—There are no population-based data on hospitalization rate for toxicity from breast cancer chemotherapy, and even large clinical trials often do not report this information. Medicare data, linked to the Surveillance, Epidemiology, and End-Results (SEER) tumor registries, are now used to assess rates of hospitalization for chemotherapy-related toxicity in a population-based setting.

Patients and Methods—A total of 35,060 women diagnosed with stages I through IV breast cancer aged ≥ 65 from 1991 through 1996 were identified from the SEER-Medicare linked program and studied. Patients were defined as being hospitalized for adverse effects of chemotherapy if there was a Medicare inpatient claim for neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy less than 7 months after diagnosis of breast cancer.

Results—More than 9% of women with breast cancer who received chemotherapy were admitted with the diagnosis of neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy, compared with 0.5% of women with breast cancer who did not receive chemotherapy. The rates for stage I to IV were 6.3%, 8.1%, 12.3%, and 13.2% in those treated with chemotherapy, and 0.4%, 0.6%, 0.7%, and 1.5% in women not treated with chemotherapy. The hospitalization rates for adverse effects increased significantly with comorbidity score and varied more than two-fold across the nine SEER areas but did not vary by age. Use of anthracycline-containing chemotherapy agents was associated with greater odds of these toxicities (eg, odds ratio, 2.53 for neutropenia; 95% confidence interval, 1.97 to 3.26).

Conclusion—This study demonstrated the feasibility of using Medicare data to assess rates of hospitalization for serious toxicity associated with cancer chemotherapy. Rates in actual practice were higher than those reported in clinical trials and did not vary by age.

The efficacy of chemotherapy for breast cancer has been well documented in numerous clinical trials.¹⁻¹³ The toxicity of cancer chemotherapy is the most important factor limiting its use.¹⁴ Clear delineation and communication of benefits and risks is an essential component of treatment decisions.

The common adverse effects caused by chemotherapy include hair loss, malaise, fatigue, nausea, vomiting, diarrhea, dehydration, neutropenia, fever, systemic infection, and thrombocytopenia.^{6,7,11,14-16} The late or long-term toxicities, depending on various agents, may include cardiac sequelae, leukemia, and second tumors.^{14,16} These side effects occur in varying degrees in different chemotherapy regimens. However, information on rates of specific toxicities associated with specific chemotherapy regimens is not easily obtainable. The Early Breast Cancer Trialists' Collaborative Group, which has produced valuable meta-analyses on

the efficacy of chemotherapy,¹⁻³ does not collect information on toxicity (Mark Clarke, MD, personal communication, March 2001). Few of the large clinical trials of chemotherapy in breast cancer (and in other cancers) have published rates of specific toxicities or rates of hospitalization from toxicities. A recent major review of toxicity from chemotherapy for breast cancer reported that hospitalization rates for infection after chemotherapy were 2% or less in four large trials (average of the four trials was 1.2%) and that “no deaths” have been reported.¹⁶ Because randomized clinical trials often have strict enrollment criteria with close monitoring and follow-up among volunteers, one might expect toxicity rates in the community that are different from those in the trials. However, to our knowledge there have been no population-based assessments of chemotherapy toxicity in breast cancer, although a recent study reported fluorouracil toxicity in colorectal cancer.¹⁷ We and others have recently shown that chemotherapy use in women aged 65 or older after diagnosis of cancer can be identified using Medicare claims data.¹⁸⁻²¹ We now use Medicare data, linked to the Surveillance, Epidemiology, and End-Results (SEER) tumor registries,²² to assess rates of hospitalization for toxicity after chemotherapy in a large population-based setting. The main objectives were to assess the feasibility of using Medicare claims data for identifying hospitalizations for serious toxicity associated with chemotherapy use in the community and to analyze the correlates of toxicity.

Patients and Methods

Data Sources

We used the merged SEER-Medicare database for women aged 65 or older diagnosed with breast cancer in 1991 through 1996 in 11 SEER areas: the metropolitan areas of San Francisco/Oakland, Detroit, Atlanta, and Seattle; Los Angeles county; the San Jose-Monterey area; and the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii.²³ These areas cover approximately 14% of the United States population. The registries ascertain all newly diagnosed breast cancer cases from multiple reporting sources.²⁴ Information includes tumor location, size, American Joint Committee on Cancer stage, demographic characteristics (age, sex, and race), and types of treatment provided less than 4 months after diagnosis.

The Medicare program covers hospital, physician, and other medical services for more than 97% of persons aged ≥ 65 .^{22,25} The Medicare claims data used in the study included the inpatient, outpatient, and physician claims.²⁵ These data were available for all beneficiaries starting in 1991, and their Medicare claims are available through 1998. Of persons aged ≥ 65 years appearing in the SEER registries from 1991 through 1996, Medicare eligibility could be identified for 94% of these cases.²²

Study Population

The study population consisted of all women aged ≥ 65 years who were diagnosed with breast cancer in 1991 through 1996 among the 11 SEER areas. For 1991 cases, the study covers only nine SEER areas because there is no information for cases diagnosed in 1991 in the Los Angeles and San Jose-Monterey areas. Excluded were women with in situ tumor and women who did not have full coverage of both Medicare Part A and Part B, or who were members of health maintenance organizations, because claims from these organizations may not be complete. These left 35,060 patients with stages I through IV breast cancer for the analysis.

Chemotherapy

The methods of identifying chemotherapy use through the Medicare claims has been discussed elsewhere.^{20,21} In brief, patients were defined as having received chemotherapy if there was a claim for chemotherapy from any of the following Medicare codes that were made less than 6 months after diagnosis: the International Classification of Diseases, Ninth Revision, Clinical

Modification (ICD-9-CM) procedure code of 9925 and V codes of V58.1, V66.2, or V67.2²⁶; the Common Procedural Terminology codes of 96400 to 96549, J9000 to J9999, and Q0083 to Q0085^{27,28}; and revenue center codes of 0331, 0332, and 0335.²⁹ There were several reasons for arbitrarily defining chemotherapy cases as those who had claims made within 6 months of diagnosis. According to the clinical guidelines, chemotherapy as a primary therapy or as an adjuvant therapy after surgery and radiation is likely to be administered within 6 months of diagnosis. In our previous studies,^{20,21} extending time periods for 9, 12, or 24 months only slightly increased the accumulated number of cases receiving chemotherapy. Our studies also suggested that chemotherapy for the recurrence of cancer or as part of the initial therapy cannot be clearly distinguished in Medicare claims.^{20,21} Therefore, chemotherapy administration was defined as within 6 months of diagnosis, which is likely to be part of initial therapy.

Adverse Effects of Chemotherapy

Adverse effects were initially defined as hospitalization for any of the following eight diagnoses within 7 months after diagnosis of breast cancer using the ICD-9-CM diagnosis codes for a hospital inpatient claim: any infection (001.0 to 139.8), neutropenia (288.0), fever (780.6), thrombocytopenia (287.4), dehydration (276.5), anemia (284.x to 285.x), delirium (780.x), or adverse effect of systemic therapy (E9331).²⁵ As a control, we also assessed hospitalizations with a diagnosis of myocardial infarction (410.x or 412.x) and hip fracture (820.x). The reason for selecting events within 7 months of diagnosis is to have a 1-month window after the administration of chemotherapy to capture immediate or early chemotherapy-related toxicity.

Comorbidity Index

Comorbidity was ascertained from Medicare claims data through diagnoses or procedures that were made between 1 year before and 1 month after the diagnosis of breast cancer. We included claims for comorbid diseases made within 1 month of diagnosis because any comorbid diseases present at that time would be likely to affect the choice of chemotherapy. We used the comorbidity index created by Charlson et al³⁰ and later modified by Romano et al³¹ using the ICD-9-CM diagnosis and procedure codes.²⁶ Both the Medicare inpatient and physician claims were searched for 19 comorbid conditions, including diabetes and heart disease but not including anemia and breast cancer (ICD-9-CM codes of 174.x).

Statistical Analyses

Because SEER reported only the month and year of diagnosis of breast cancer, we arbitrarily defined the day of diagnosis in SEER as the 15th of the month. The date of administration of chemotherapy from inpatient claims was defined as the date of admission. For outpatient and physician claims, the date of administration of chemotherapy was defined as the earliest date of service. The χ^2 statistic was used to test the significance of hospitalization for an individual toxicity between women who received chemotherapy and those who did not. A multivariate logistic regression analysis for the risk of being hospitalized for any toxicity was also performed in women who received chemotherapy compared with those who did not. These analyses adjusted for age, race, tumor stage, and comorbidity indices, which are considered to likely affect the use of chemotherapy in women with breast cancer. The backward logistic regression approach was used to select the significant predictors for hospitalization of each adverse effect. All computer programming and analyses were completed using the SAS system (SAS Institute, Inc, Cary, NC).³²

Results

Initially, eight groups of diagnoses that might plausibly occur as a serious toxicity (ie, resulting in hospitalization) of chemotherapy administration were assessed. These diagnoses were infection, neutropenia, fever, thrombocytopenia, dehydration, anemia, delirium, and the ICD-9 code for adverse effect of systemic therapy. Table 1 lists the percentages of patients who were hospitalized for these diagnoses within 7 months after diagnosis of breast cancer, stratified by whether or not they received chemotherapy within 6 months of diagnosis. Among women receiving chemotherapy, 20.1% were admitted to the hospital with one or more of these eight diagnoses, compared with 8.6% of women not receiving chemotherapy ($P < .001$). Some diagnoses had greater specificity for chemotherapy use than did others. In particular, women not receiving chemotherapy had low rates of hospitalization for neutropenia, fever, thrombocytopenia, or unspecified adverse effect of systemic therapy, compared with women who received chemotherapy. For example, 7% of women who received chemotherapy were hospitalized with neutropenia, compared with 0.1% of women who did not receive chemotherapy. As a control, we also assessed hospitalization rates for hip fracture and myocardial infarction. There were no significant differences in hospitalization rates for these two conditions between the women receiving chemotherapy and those who did not.

Table 2 lists the odds of hospitalization with any of the eight diagnoses listed in Table 1 and also for any of the four diagnoses (neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy), as a function of receipt of chemotherapy. After controlling for other factors that might have affected the likelihood of hospitalization, women who received chemotherapy were more than twice as likely to be admitted with any of these eight diagnoses than women not receiving chemotherapy. When diagnoses were restricted to neutropenia, fever, thrombocytopenia, and adverse effect of systemic therapy, women who received chemotherapy were 14 times more likely to be hospitalized with any of these four diagnoses than women who did not receive chemotherapy. The rate of hospitalization for toxicity was higher in women with more advanced tumor stages.

Approximately 5% (40 of 831) of those hospitalized for the eight diagnoses listed in Table 2 died during that hospitalization. Overall, 40 (0.97%) of the 4,134 women who received chemotherapy died in hospital with one of the eight toxicity diagnoses, compared with 0.40% of women who did not receive chemotherapy ($P \leq .001$). Nobody died among those with stage I tumor. The death rates were 0.18%, 1.59%, and 5.12%, respectively, in women with stage II, III, and IV disease who received chemotherapy. Similarly, 18 (0.44%) of the 4,134 women who received chemotherapy died during a hospitalization with one of the four toxicity-associated diagnoses, compared with a death rate of 0.03% for women not receiving chemotherapy ($P \leq .001$). The death rates for women with stages II, III, and IV tumors who received chemotherapy were 0.09%, 1.06%, and 1.71%, respectively.

We next examined, among women receiving chemotherapy, what characteristics predicted hospitalization with one of the four toxicity diagnoses closely associated with chemotherapy use. Table 3 lists the rates and a multivariate analysis of predictors of hospitalization with any of these four diagnoses. The risk of hospitalization for these toxicities did not vary significantly by age or race. However, the risk increased with tumor stage and comorbidity score. There was also geographic variation in the hospitalization rates for those adverse effects, with some SEER areas having a more than two-fold higher hospitalization rate compared with others.

Table 4 lists the significant predictors for hospitalization for each of the individual diagnoses that were related to chemotherapy. In these analyses, the type of chemotherapeutic drug was included (anthracycline v others), plus those factors listed in Table 3. The results were obtained from a series of backward logistic regressions, which left only significant factors in the final

model. Some interesting patterns emerged. For example, advanced age predicted hospitalization for neutropenia, dehydration, and anemia, but not the other toxicities. Advanced stage at diagnosis was associated with increased odds of hospitalization for all of the diagnoses except fever and unspecified adverse effect of systemic therapy. Comorbidity was associated with significantly greater odds of hospitalization for a diagnosis of dehydration, and African-American race was associated with increased odds of hospitalization for anemia. There was geographic variation in odds of hospitalization for most of the specific toxicities. Finally, use of anthracycline chemotherapy agents (doxorubicin and mitoxantrone), which were used in 32% of women who received chemotherapy, was associated with greater odds of neutropenia, thrombocytopenia, infection, fever, delirium, and unspecified adverse effect of systemic therapy.

Finally, we conducted regression analyses similar to those in Table 4, examining predictors of death during a hospitalization with any of the four toxicity-related diagnoses for all women in the sample (Table 5). Both receipt of chemotherapy and advanced tumor stage at diagnosis were strongly predictive of death during hospitalization for toxicity.

Discussion

This study represents an examination of the feasibility of using Medicare data to assess serious toxicity from chemotherapy received by older women with breast cancer in the community. One in five women with breast cancer who received chemotherapy was admitted with one or more of eight diagnoses (infection, neutropenia, fever, thrombocytopenia, dehydration, anemia, delirium, and adverse effect of systemic therapy), whereas only 8.6% of women with breast cancer who did not receive chemotherapy were admitted. When the comparison was restricted to hospitalization with any of four toxicity-related diagnoses (neutropenia, fever, thrombocytopenia, and adverse effect of systemic therapy), the corresponding hospitalization rates were 9.2% for women who received chemotherapy versus 0.5% for those who did not. The hospitalization rates for adverse effects increased significantly with tumor stage and comorbidity scores, and varied more than two-fold across SEER regions. Use of anthracycline-containing agents was associated with greater odds of toxicities. Advanced tumor stage was a significant predictor of death during hospitalization for toxicity-associated diagnoses. Among those women aged 65 and older, advanced age (ie, age 75 to 79 or ≥ 80 v 65 to 69 years) was not associated with an increased rate of hospitalization or death rate from toxicity after chemotherapy.

There are several potential advantages of using Medicare data to assess toxicity from cancer chemotherapy. First, the data are population-based, which should give a more accurate picture of actual rates of toxicity in the community than would data from clinical trials. Second, the large number of patients available in the SEER-Medicare merged database allow for estimation of toxicity rates by specific patient and tumor characteristics. Third, such data may point to potential issues of quality control. For example, it is unclear why the toxicity rates vary significantly by geographic area after controlling for patient and tumor characteristics (Table 3). Fourth, such studies may allow investigators to uncover unusual or unexpected patterns of toxicity. For example, the increased rate of anemia for African-Americans after chemotherapy may represent a chance association, but it should be explored. Fifth, the use of existing administrative data is considerably less costly than would be a determination of toxicity rates by chart review.

Age is a strong factor in determining treatment for patients with cancer,³³⁻³⁹ particularly in the choice of chemotherapy for breast cancer, where the efficacy of adjuvant chemotherapy for breast cancer decreases with advancing age.^{1-3,20,21} Among physicians and patients, there is a common perception that older patients have a greater risk of toxicity from chemotherapy.

⁴⁰ However, several studies showed no effect of age on the frequency of chemotherapy-related toxicity,⁴⁰⁻⁴⁴ as was the case in our current study.

To assess the frequency and severity of adverse events, randomized trials with adequate sample size offer a unique opportunity, because these trials have the most comprehensive and systematic accumulation of pertinent information in a controlled setting. However, information on toxicity is scarce in older women receiving chemotherapy. The International Breast Cancer Study Group recently reported the toxicity from combination chemotherapy (cyclophosphamide, methotrexate, and fluorouracil) in 299 postmenopausal women with operable node-positive breast cancer.¹⁵ Among the 79 women aged 65 or older, there were no life-threatening toxicities. The rates of serious toxicity from chemotherapy for breast cancer are generally reported to be somewhat higher in older than in younger patients,⁴⁰⁻⁴² although it is difficult to extract data on hospitalization or other consequences of toxicity from those reports. In women with advanced breast cancer, older patients tolerate the toxicity as well as younger patients.^{43,44} In general, the rates of life-threatening toxicity from the published trials were considerably lower than what were found in our study. Reasons for the lower toxicity rates in clinical trials include selection bias, whereby healthier and better-educated women tend to participate disproportionately in clinical trials. Also, the quality of medical care and follow-up may be better in the trials, resulting in earlier recognition of a toxicity with avoidance of subsequent hospitalization.

It is important to point out several limitations in this study. First, a major issue related to toxicity is dose of chemotherapy, and there is limited information about dose in the Medicare data. A second limitation is that we only could generate data on life-threatening toxicities or death, not the milder forms of toxicity that can be assessed in clinical trials. Third, we cannot establish with certainty whether a given toxicity-related diagnosis was the reason for hospitalization or occurred during hospitalization for another reason. Fourth, there are difficulties in determining drug-specific toxicity. Chemotherapy is normally used in combination fashion (two or three types of chemotherapy agents within a cycle). Our findings that the use of anthracycline-containing agents was associated with greater risk of toxicities supported what was observed in other studies.⁸ Fifth, we have no information on rate of hospitalization for toxicity in women younger than age 65. Sixth, there was a lack of information in Medicare claims data on quality of life and physical function for the elderly. Finally, an observational study cannot prove a causal relationship between chemotherapy use and hospitalizations with a toxicity-associated diagnosis. In contrast, the association remained after controlling for other factors that might affect risk of hospitalization. In general, once stage at diagnosis is controlled for, one would expect those who received chemotherapy in the community to be somewhat healthier than those who did not, which would bias the analysis against finding the association.

It is difficult to compare our results directly with clinical trials. Many of the breast cancer chemotherapy trials did not report data on toxicity. Those trials that do report toxicity use different grading systems (eg, from the World Health Organization or the National Cancer Institute). These grading systems are based either on laboratory values (eg, grade 4 bone marrow toxicity by the National Cancer Institute criteria is defined as < 500 granulocytes/ mm^3), or by simple description (eg, grade 3 infection toxicity is defined as “severe”), without specific reference to whether hospitalization was required, although “life-threatening” toxicity usually requires hospitalization.⁴⁵ Lack of complete information on toxicity is not unique to trials of chemotherapy. In a review of 192 randomized drug trials of all types, laboratory-determined toxicity was adequately defined in only 29%, and adequate reporting of clinical adverse events was seen in only 39%.⁴⁶ Obtaining reliable information on adverse effects is even more problematic in community practice. Of the 3% to 11% hospital admissions that are attributed to adverse drug reactions, few are reported to the Food and Drug Administration.⁴⁷

Currently, none of the existing methods for identifying adverse drug events is sufficient on its own.⁴⁸ Medical chart review is effective for research but is too costly for routine clinical monitoring. The computerized Medicare claims data offers a promising and less expensive way of obtaining this information. For postmarket surveillance of cancer drug therapy in the community, Medicare data may provide information on immediate or short-term toxicities and perhaps also on late serious toxicities, which are difficult to identify in clinical trials. For complete information concerning chemotherapy in older patients, supplementing the data from randomized clinical trials with analyses of Medicare claims data may produce the best estimates.

In conclusion, this study demonstrated the feasibility of using Medicare data to assess rates of hospitalization for serious toxicity associated with cancer chemotherapy use in the community. It showed that the rates of hospitalizations for toxicity in actual practice were higher than those reported in clinical trials and that age did not significantly impact on these rates when other factors were controlled for.

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Table 1
Hospitalization for Adverse Effects Possibly Related to Chemotherapy in Women With Stages I-IV Breast Cancer Diagnosed From 1991 Through 1996 in SEER Who Received Chemotherapy, Compared With Those Patients Not Receiving Chemotherapy

Discharge Diagnosis for Women Hospitalized (ICD-9-CM code)	Women Hospitalized With Specific Discharge Diagnosis Within 7 Months of Breast Cancer Diagnosis				P
	Women Receiving Chemotherapy Within 6 Months of Diagnosis (n = 4,134)		Women Not Receiving Chemotherapy Within 6 Months of Diagnosis (n = 30,926)		
	No.	%	No.	%	
Infection (001.0-139.8)	278	6.7	903	2.9	< .001
Neutropenia (288.0)	288	7.0	35	0.1	< .001
Dehydration (276.5)	178	4.3	486	1.6	< .001
Fever (780.6)	120	2.9	102	0.3	< .001
Anemia (284.0-285.9)	380	9.2	1187	3.8	< .001
Thrombocytopenia (287.4)	25	0.6	14	0.1	< .001
Delirium (780.x)	198	4.8	527	1.7	< .001
Unspecified adverse effect of systemic therapy (E9331)	125	3.0	11	0.0	< .001
Any of the above	831	20.1	2,653	8.6	< .001
Myocardial infarction (410.x or 412.x)	53	1.3	418	1.4	.715
Hip fracture (820.x)	18	0.4	182	0.6	.219

Effect of Chemotherapy Use on Hospitalization With Toxicity-Related Diagnosis in Women With Stages I-IV Breast Cancer From 1991 Through 1996

	Cases Having Toxicity				Adjusted OR* of Being Hospitalized With Toxicity-Related Diagnosis in Women Receiving Chemotherapy, Compared With Those Without	95% CI	
	Women Receiving Chemotherapy Within 6 Months of Diagnosis (n = 4,134)		Women Not Receiving Chemotherapy Within 6 Months of Diagnosis (n = 30,926)				
	No.	%	No.	%			
Any of eight diagnoses [†]							
	All stages	831	20.1	2,653	8.6	2.33	2.11-2.58
	Stage I	110	17.2	1,305	7.1	2.95	2.37-3.67
	Stage II	369	16.2	948	9.4	2.05	1.78-2.37
	Stage III	201	26.6	197	13.6	2.68	2.10-3.44
Any of four diagnoses [‡]	Stage IV	151	32.2	203	22.7	1.71	1.31-2.23
	All stages	379	9.2	153	0.5	14.39	11.39-18.17
	Stage I	40	6.3	67	0.4	16.65	10.94-25.33
	Stage II	184	8.1	63	0.6	13.06	9.53-17.89
Stage III	93	12.3	11	0.7	22.57	11.34-44.90	
	Stage IV	62	13.2	12	1.5	9.13	4.86-17.17

NOTE. Tumor stage-specific rate of chemotherapy use was 3.3%, 18.4%, 34.2%, and 34.4%, respectively, for stages I-IV.²¹

* Adjusted for age (65-69, 70-74, 75+), race (white, black, and others), comorbidity scores (0, 1, ≥ 2), nine SEER areas (San Francisco/Oakland was combined with Los Angeles county and the San Jose-Monterey area in California), and stage (I, II, III, and IV, only adjusted in analyses of all stages combined).

† Including any of the following eight discharge diagnoses: infection, neutropenia, dehydration, fever, anemia, thrombocytopenia, delirium, or adverse effect of systemic therapy.

‡ Including any of the following four discharge diagnoses: neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy.

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3
Prevalence and Risk of Hospitalization for Adverse Events Among Women Who Received Chemotherapy for Stages I-IV Breast Cancer Diagnosed From 1991 Through 1996, by Patient and Tumor Characteristics

Patient and Tumor Characteristic	No. of Cases Receiving Chemotherapy [*]	Cases With Hospitalization for Chemotherapy-Related Adverse Effects (%) [†]	OR of Being Hospitalized for Chemotherapy-Related Adverse Effects [‡]	
			OR	95% CI
Total patients	4,134	9.2	—	—
Age				
65-69 years	1,819	9.2	1	Reference
70-74 years	1,333	9.8	1.08	0.85-1.38
75-79 years	687	7.1	0.76	0.55-1.07
80+ years	295	10.9	1.14	0.76-1.72
Race				
White	3,684	9.1	1	Reference
Black	299	9.4	1.00	0.65-1.54
Other	151	10.6	1.03	0.47-2.22
Tumor stage				
I	638	6.3	1	Reference
II	2,272	8.1	1.28	0.86-1.91
III	755	12.3	2.26	1.41-3.62
IV	469	13.2	2.42	1.48-3.96
Comorbidity index				
0	1,721	7.9	1	Reference
1	326	9.8	1.43	0.95-2.16
2+	2,087	10.1	1.27	1.00-1.60
SEER area				
A	1,029	7.1	1	Reference
B	666	7.4	1.02	0.69-1.49
C	746	8.9	1.23	0.86-1.75
D	91	15.4	2.25	0.99-5.10
E	552	14.5	2.26	1.60-3.19
F	142	7.8	1.08	0.56-2.11
G	472	8.3	1.10	0.73-1.67
H	159	9.4	1.40	0.77-2.52
K	277	11.6	1.67	1.07-2.63

* Defined as having Medicare claims for chemotherapy within 6 months of diagnosis of breast cancer.

[†] Defined as having Medicare claims for hospitalization for any of the following four discharge diagnoses: neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy, within 7 months of diagnosis of breast cancer.

[‡] Adjusted for other factors listed in the table, including nine SEER areas (San Francisco/Oakland was combined with Los Angeles county and the San Jose-Monterey area in California).

Table 4
Summary of Significant Predictors of Hospitalization for Specific Toxicity in Women With Breast Cancer From 1991 Through 1996 Who Received Chemotherapy (n = 4,134)

Discharge Diagnosis	Significant Predictor	OR*	95% CI
Neutropenia	Age (65-69 as reference)		
	70-74 years	1.31	1.02-1.69
	Stage (stage I as reference)		
	Stage III	1.44	1.07-1.94
	Stage IV	1.56	1.10-2.21
	Type of chemotherapy agent		
	Anthracycline agents (yes v no)	2.53	1.97-3.26
Thrombocytopenia	SEER area (area A as reference)		
	Area D	2.08	1.10-3.93
	Area E	2.33	1.73-3.15
Dehydration	Type of chemotherapy agents		
	Anthracycline agents (yes v no)	2.67	1.21-5.91
	Age (65-69 as reference)		
	70-74 years	1.51	1.03-2.20
	75+ years	2.20	1.46-3.32
	Stage (stage I as reference)		
	Stage II	0.66	0.46-0.95
Infection	Stage IV	2.26	1.52-3.37
	Comorbidity scores (0 as reference)		
	1	1.98	1.17-3.37
	≥2	1.57	1.12-2.20
	Stage (stage I as reference)		
	Stage II	0.61	0.47-0.78
	Type of chemotherapy agent		
Fever	Anthracycline agents (yes v no)	1.35	1.04-1.73
	SEER area (area A as reference)		
	Area D	1.44	1.06-1.97
	Area E	1.99	1.01-3.93
	Area K	1.80	1.29-2.51
	Type of chemotherapy agent		
	Anthracycline agents (yes v no)	2.38	1.64-3.44
Anemia	SEER area (area A as reference)		
	Area B	1.70	1.08-2.69
	Area D	3.58	1.66-7.72
	Area K	2.11	1.18-3.75
	Age (65-69 as reference)		
	75+ years	1.48	1.17-1.87
	Race		
Delirium	Black (v white)	1.71	1.20-2.46
	Stage (stage I as reference)		
	Stage III	2.19	1.71-2.81
	Stage IV	2.03	1.49-2.75
	SEER area (area A as reference)		
	Area B	0.67	0.47-0.95
	Area E	1.62	1.21-2.18
Unspecified adverse effect of systemic therapy	Area H	1.71	1.04-2.80
	Stage (stage I as reference)		
	Stage IV	1.60	1.09-2.34
	Type of chemotherapy agent		
	Anthracycline agents (yes v no)	1.66	1.24-2.22
	SEER area (area A as reference)		
	Area D	2.35	1.19-4.63
	Type of chemotherapy agent		
	Anthracycline agents (yes v no)	1.98	1.38-2.85
	SEER area (area A as reference)		
	Area D	4.34	1.90-9.94
	Area E	4.09	2.61-6.42
	Area G	2.56	1.07-6.10
	Area H	2.73	1.21-6.15

* Adjusted in a multivariate model for age (65-69, 70-74, 75+), race (white, black, and others), stage (I, II, III, and IV), comorbidity scores (0, 1, ≥ 2), nine SEER areas (San Francisco/Oakland was combined with Los Angeles county and the San Jose-Monterey area in California), and types of chemotherapy agent (yes or no), including anthracycline agents (doxorubicin and mitoxantrone) and nonanthracycline agents (cyclophosphamide, fluorouracil, methotrexate, and paclitaxel [Taxol]).

Table 5
Predictors of Being Discharged Dead With a Toxicity-Related Diagnosis in Women With Breast Cancer From 1991 Through 1996*

Predictor	OR [†]	95% CI
Receipt of chemotherapy (v nonuser)	5.84	2.55-13.37
Stage (stage II as reference)		
Stage III	9.80	3.67-26.17
Stage IV	15.88	5.94-42.45

* Including any of the following four discharge diagnoses: neutropenia, fever, thrombocytopenia, or adverse effect of systemic therapy.

[†] Adjusted in a multivariate model for age (65-69, 70-74, 75+), race (white, black, and others), stage (I, II, III, and IV), comorbidity scores (0, 1, ≥ 2), nine SEER areas (San Francisco/Oakland was combined with Los Angeles county and the San Jose-Monterey area in California), and receipt of chemotherapy agent (yes or no).